REMARKS

Applicants have canceled claims 4-6, 28-29, and 39-40 without prejudice to continued prosecution. Claims 26 and 27 have been amended to recite that the dosage of α-interferon is 500,000 U/m^2 or less per day and at least about 250,000 U/m^2 per day. Support for this amendment can be found, for example, at page 5, lines 19-26 and page 11, lines 16-20. No new matter has been introduced. Applicants respectfully request reconsideration and allowance of claims 8-12, 18, 21-22, 26-27, and 30-38.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 4-6, 8, 18, 21, 22, 26, 39 and 40, under 35 U.S.C. § 102(e) as being anticipated by Tovey et al. (U.S. Patent No. 5,997,858). The Examiner rejected claims 9-12 under 35 U.S.C. § 102(e) as being anticipated by the Tovey et al. patent, in light of the Brittenden et al. reference (Cancer, 1996, 77(7):1226-1243). The Examiner asserted that since "Tovey teaches methods using dosages that are within the range of those recited in claims dependent from claim 26, Tovey inherently teaches the methods of claim 26 and the methods of the claims dependent from claim 26." The Examiner also asserted that "the ability of alpha-interferon to increase NK-lymphocyte activity is an inherent effect of the administration of alpha-interferon, as evidenced by the teachings of Brittenden." Brittenden was characterized as teaching that alpha-interferon enhances NK cell activity and that alpha-interferon can be used in the treatment of renal carcinoma.

Amended claim 26 recites that the immunostimulatory dosage is 500,000 U/m^2 or less per day and at least about 250,000 U/m^2 per day. The Tovey et al. patent does not inherently disclose determining the baseline natural killer lymphocyte cytotoxicity then administering to the patient an immunostimulatory dosage of α-interferon that is about 500,000 U/m^2 day or less, but at least about 250,000 U/ m^2 per day. Rather, the Tovey et al. patent indicates an amount of α-interferon ranging from 5000 IU to 20x10^6 IU per 70 kg man is administered to the mammal, as long as the amount of α-interferon does not induce a pathological response when administered parenterally. Preferred ranges are 1 x 10^4 U to about 20 x 10^6 U and 1 x 10^4 to 1 x 10^6 U of α-interferon. See, column 2, lines 48-53 of the Tovey et al. patent. The Brittenden reference does not disclose any particular dosages of α-interferon. The Brittenden reference is a review of the

role of natural killer cells cytotoxicity and lymphokine-activated killer activity in patients with cancer.

The Tovey et al. patent, alone or in view of the Brittenden reference, does not disclose determining a baseline level of natural killer cytotoxicity, then administering the claimed amount of α-interferon. While the Tovey et al. patent discloses administering amounts of α-interferon to a patient, the disclosed amounts of the Tovey et al. patent do not allow one of ordinary skill in the art to envisage using 500,000 U/m^2 or less per day and at least about 250,000 U/m^2 per day of α-interferon. In view of the above remarks, the Examiner is requested to withdraw the rejection under 35 U.S.C. §102(e).

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 9 and 40 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner asserted that claims 9 and 40 recite limitations already present in claims 26 and 6, respectively. Claim 26 has been amended to delete the limitations recited in claim 9. Thus, claim 9 does not contain the same limitations as claim 26. Claim 40 has been canceled. The Examiner is requested to withdraw the rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 27-38 under 35 U.S.C. § 103(a) as being unpatentable over Markovic et al. (Int. J. Cancer, 1990, 45:788-794) in view of Edwards et al. (Cancer Res., 1984, 44:3135-3139). The Examiner characterized the Markovic et al. reference as teaching that "alpha-interferon acts to increase NK lymphocyte cytotoxicity and that this is a desired effect in the surgical treatment of cancer because of the presence of disseminated tumor foci following surgical excision of the primary tumor. Markovic also teaches a method for the surgical removal of a tumor in mice, where the mice were treated prior to surgery with alpha interferon." The Markovic et al. reference was characterized as failing to teach the dosages necessary to increase NK lymphocyte cytotoxicity by at least 50% or 75%. Edwards was deemed to teach that a dose of 1.65 x 10^6 U increased NK lymphocyte cytotoxicity by about 100%. The Examiner asserted

that it would be obvious to have used the teachings of Markovic to make a method for treating humans by combining the teachings of Markovic with the teachings of Edwards.

Markovic et al. administered α-interferon to mice with primary tumors prior to excision of the tumors. It was observed that tumor-associated mortality was limited and that administration prior to surgery was more effective than administration after surgery.

The Edwards et al. reference examined activation of human NK cells clinically by administering low dosages of IFN-αD (0.083 or 0.25 million units) or IFN-αA (1.7 or 5.0 million units) intramuscularly. See page 3135 pf the Edwards et al. reference. The larger IFN dose was considered to be less effective in boosting NK cell activity. See page 3136 of the Edwards et al. reference.

The combination of the Markovic et al. and Edwards et al. references does not teach or suggest determining a baseline level of natural killer cytotoxicity then administering the claimed amount of α-interferon. Based on the combination of the Markovic et al. reference and Edwards et al. reference, one of ordinary skill in the art would not be able to specifically envisage using 500,000 U/m^2 or less per day and at least about 250,000 U/m^2 per day of α-interferon for treating human patients. Thus, the combination of the Markovic et al. and Edwards et al. references does not teach or suggest the claimed invention. The Examiner is requested to withdraw the rejection under 35 U.S.C. §103.

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment.

Applicant : Svetomir N. Markovic
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Applicant asks that claims 8-12, 18, 21-22, 26-27, and 30-38 be allowed. No fees are due as this response is being filed before the end of the shortened statutory period. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 10/15/02

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Version with markings to show changes made

In the claims:

Claims 4-6, 28-29, and 39-40 have been cancelled.

Claims 26 and 27 have been amended as follows:

26. (Four times amended) A method for stimulating the immune system of a human patient having a non-resectable malignant tumor, said method comprising

a) determining the natural killer lymphocyte cytotoxicity of said patient to provide a baseline natural killer lymphocyte cytotoxicity;

b) administering an immunostimulatory dosage of an α-interferon composition to said patient, wherein said immunostimulatory dosage [increases the natural killer lymphocyte cytotoxicity of said patient at least 50% above said baseline] is 500,000 U/m^2 or less per day and at least about 250,000 U/m^2 per day; and

c) treating said patient with effective non-surgical medical methodologies to diminish said tumor.

27. (Amended) A method for stimulating the immune system of a human patient having a resectable malignant tumor, said method comprising:

a) determining the natural killer lymphocyte cytotoxicity of said patient to provide a baseline natural killer lymphocyte cytotoxicity;

b) administering an immunostimulatory dosage of an α-interferon composition to said patient, wherein said immunostimulatory dosage [increases the natural killer lymphocyte cytotoxicity of said patient at least 50% above said baseline] is 500,000 U/m^2 or less per day and at least about 250,000 U/m^2 per day; and

c) surgically resecting said malignant tumor.